

## NON-SYSTEMATIC REVIEW

## Pediatrics

# An overview of the COVID-19 complications in paediatric population: A pandemic dilemma

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**Abstract**

**Aim:** The primary objective of this article is to understand the various complications caused by the coronavirus in the paediatric population.

**Method:** An electronic search was conducted using PubMed and incorporated forward and backward research methods on clinical trials, case reports, case series, guidelines and reports from the centre for disease control and prevention (CDC), and the keywords included COVID-19, paediatrics, multisystem inflammatory syndrome in children (MIS-C), complications, acute kidney injury and heart failure. Secondary resources included one study from preprint servers ([www.preprints.org](http://www.preprints.org)), last search 8 May 2021, with notion of nonpeer review status. Data were collected and analysed to stay current with the most recent alerts and guidelines for the best care for children during the COVID-19 pandemic.

**Results:** Evaluation and analysis of literature revealed MIS-C to be the most prevalent followed by neurological complications. Whereas the least prevalent were septic shock and ophthalmic complications.

**Conclusion:** Even though COVID-19 is known to be a less severe in the paediatric population, the complications of the virus have caused a great deal of stress to the paediatric patients' parents and paediatricians worldwide, and hence, emphasis should be given to the management of coronavirus complications in paediatrics.

## 1 | INTRODUCTION

Human coronavirus responsible for most commonly infecting children belongs to the OC43, HKU1, NL63 and 229E species distributed throughout the world. Although paediatrics are less prone to acquire the infection as compared with the adult population and, hence, tend to appear with milder symptoms.<sup>1</sup> This could be due to that children's nasal epithelium expresses lower levels of the ACE2 protein (where SARS-CoV-2 joins cells), with expression increasing as they get older.<sup>2,3</sup> The clinical significance of the difference is unknown, particularly because there does not appear to be a connection between ACE2 expression and viral load.<sup>2</sup> There have been observations of T-cell-mediated immunity cross-reactivity to COVID-19 dependent on prior exposure to other, less serious human coronaviruses (hCoV).<sup>4</sup> Symptoms in children include fever,

rhinorrhoea, sore throat and nasal congestion and fatigue; some gastrointestinal manifestations like vomiting, abdominal pain, nausea and diarrhoea have also been reported.<sup>5-10</sup> A good prognosis is seen in the majority of the paediatrics having an average recovery time of 1-2 weeks from the onset of infection.<sup>5-8</sup>

Available evidence says that paediatrics under the age of 5 years suffering from moderate to a mild form of infection have a higher amount of viral RNA particles in their nasopharynx as compared with children >5 years and adults. Due to behavioural tendencies and close contact with others in daycare services or schools, concerns are being raised, making this population a critical target for immunisation for the prevention of spread.<sup>11</sup>

The greatest prevailing clinical presentations reported in children were seen to be identical to the adult population. Many children were seen with symptoms such as delirium, cold and difficulty

in breathing.<sup>12-18</sup> Aching throat, myalgia, nose blockage and headache were also reported. Although gastrointestinal (GI) symptoms were noted less frequently, the occurred symptoms included pain in the abdomen, nausea or vomiting and loose motions.<sup>15,19,20</sup>

Loss of smell and loss of taste in the adult population have been often noted in coronavirus patients, seldom as the primary and only clinical presentation.<sup>21-24</sup> Due to the challenges of obtaining such symptoms in children, these presentations have had negative reports.

In chronically ill children<sup>25</sup> and adults<sup>26,27</sup> with COVID19, hypoalbuminemia is thought to be an indicator of worse outcomes. Hypoalbuminemia has been shown to be an indicator of vascular disease and mortality in previous studies.<sup>26,27</sup> Children with a moderate type of COVID-19 have been confirmed to have hypoalbuminemia. We did not find hypoalbuminemia in children with moderate to mild COVID19, contrary to an earlier report,<sup>28</sup> but we did find hypoalbuminemia in children with potentially life-threatening disorders, such as those with multisystem inflammatory syndrome.<sup>29</sup> This variation in behaviour may be due to the severity of the inflammatory response, which is likely to be higher in patients with multisystem inflammatory syndrome. Like those with extreme COVID-19 who need intensive care, these infants have hypoalbuminemia, which is defined by a high inflammatory status and albumin levels of less than 3.0 g/dL.<sup>30</sup>

A literature search was conducted and incorporated forward and backward research methods from December 2020 to April 2021. The complications caused by the recent coronavirus infection in paediatric patients were then reviewed, and the data was compiled, summarised and discussed.

## 2 | COMPLICATIONS IN PAEDIATRIC POPULATION

### 2.1 | Long covid

Long COVID has been found to be a significant complication in paediatrics, according to a cross-sectional study conducted in Italy. Amongst the 129 patients amongst in the study, 52.7% reported of at least one recurring symptoms even after 120 days from diagnosis of the infection, and 42.6% experienced impairments in routine activities due to these symptoms, which include headache, joint and muscle pain, respiratory problems, palpitations and fatigue.<sup>31,32</sup> Assessment of the patients was conducted on average  $162.5 \pm 113.7$  days post-COVID-19 microbiological diagnosis. The most common symptom was found to be insomnia (18.6%) followed by respiratory symptoms (like chest tightness and pain) (14.7%), nasal congestion (12.4%), fatigue (10.8%), muscle pain (10.1%) and joint pain (6.9%) being the least common amongst the most often reported symptoms. Conclusively, 41.8% of patients had a complete recovery, whereas 35.7% presented with 1 or 2 symptoms and 22.5% presented with three or more symptoms.<sup>33</sup>

### How was the information gathered?

A search was conducted using PubMed for studies with date limits ranging from April 2020 to April 2021. The key words included COVID-19, paediatrics, multisystem inflammatory syndrome in children (MIS-C), complications, acute kidney injury and heart failure. The articles were selected for inclusion by the authors on the basis of relevance. Secondary resources included one study from preprint servers ([www.preprints.org](http://www.preprints.org)), last search 8 May 2021, with notion of nonpeer review status.

### Take home message for the clinicians

- Although paediatrics are less prone to get infected by the COVID-19 infection, the mutations of the virus make the complications unforeseeable.
- Paediatricians are recommended to prioritise the treatment in paediatrics to reduce the risk of morbidity and mortality.

Between January 2020 and January 2021, 510 children (56.3% females) were infected. Twenty-two (4.3%) of the children were admitted after they were first infected with COVID-19. COVID-19 was shown to be persistent in children for an average of 8.2 months. Tiredness and exhaustion in 87.1% of study, fatigue (80.4%), headache (78.6%), abdominal discomfort (75.9%), muscle and joint pain (60.6%), post-exertional malaise (53.7%) and rash (53.7%) were the other common signs (52.4%). At least four signs were present in 94.9% of the children. A total of 25.3% of the children reported ongoing COVID-19 illness symptoms, 49.4% had apparent healing times before symptoms reappeared, and 19.0% had an extended course of well-being before symptoms reappeared. While just 10.0% have returned to their previous rate of regular activity. The patients' parents have identified a high incidence of neuropsychiatric symptoms in their children.<sup>34</sup>

### 2.2 | Multisystem inflammatory syndrome in children

According to The Centers for Disease Control and Prevention (CDC) case definition,<sup>35</sup> a case with multisystem inflammatory syndrome in children (MIS-C) was defined as follows:

- An individual aged <21 years presenting with fever, laboratory evidence of inflammation including an elevated level of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH) or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin and evidence of clinically severe illness requiring hospitalisation, with more than two multisystem organ

involvement (cardiac, renal, respiratory, hematologic, GI, dermatologic or neurological);

- No alternative plausible diagnoses and
- Positive for current or recent SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) or serology test.

Physicians alongside antibody testing and clinical evaluation may also prescribe lab tests, including blood and urine tests, to check for elevated rates of inflammatory parameters. Imaging such as a chest X-ray, an echocardiogram, an abdominal ultrasound or a CT scan and other tests based on the clinical signs and symptoms of MIS-C are recommended for diagnosis.<sup>35</sup>

According to news from New York, 102 cases of MIS-C were diagnosed, amongst which three children between 5 and 18 years of age passed away. The focal point of this surge was found to be New York City, reporting 50 cases.<sup>36</sup> Kawasaki shock syndrome and MIS-C have some common features between them in physiology; however, heart dysfunction was observed in all patients with low systolic BP.<sup>30</sup>

Evidence from an Iranian study conducted in three paediatric hospitals reported details of 45 children that met the inclusion criteria for MIS-C. The children were on average 7 years old (ranging from 10 months to 17 years), and 53% of them were male. The most common presenting symptoms are fever 91%, stomach pain 58%, nausea/vomiting 51%, mucocutaneous rash 53%, conjunctivitis 51% and hands and feet inflammation 40% with a median time of symptoms of 5 days prior to presentation.

The majority of MIS-C patients (69%) had Kawasaki-like disease, whereas 20% had sepsis-like diseases, and 11% had toxic shock-like cases. Abdominal pain was more common in Kawasaki-like conditions and sepsis like conditions than in toxic shock-like conditions.

Many cases had significantly increased inflammatory parameters such as ESR and CRP, which is used as an alternate marker for Interleukin-6 (IL-6), at the time of admission (97%). Hypoalbuminemia was observed in 20 of the 31 patients (64.5%), and hyponatremia was found in 64% of the reports.<sup>37</sup>

Evidence from another study conducted in the United States reported 186 patients suffering from MIS-C, with the peak incidence being observed when the action of the COVID-19 virus was declining.<sup>29</sup>

The majority of the patients had involvement of a minimum of four organ systems. The most frequently involved systems included respiratory (70%), mucocutaneous (74%), haematological (76%), cardiovascular (80%) and GI system (92%).<sup>29</sup>

Additionally, MIS-C has been proved to play a key role in the development of other complications proven by a study recruiting one 49 patients showing cardiovascular involvement, amongst which 48% required supportive treatment with vasoactive agents. An elevation of BNP and troponin levels were the major findings. A minimum of one echocardiogram was taken for almost all patients (91%). Incidence of coronary artery aneurysms was found to be 8% of the

total study population. A total of 59% of the patients showed respiratory deficits, whereas 85% had no evidence of underlying conditions relating to the respiratory system. Conclusively, 17% of the patients required non-invasive mechanical ventilation, and 20% required invasive mechanical ventilation. A total of 92% of the patients showed alteration in inflammatory marker suggesting inflammation inclusive of high levels of CRP or ESR, ferritin, fibrinogen, alanine aminotransferase level and D-dimer levels, and others included anaemia, neutrophilia, thrombocytopenia, hypoalbuminemia and prolongation of international normalised ratio.<sup>29</sup>

## 2.3 | Cardiovascular complications

Data from a Chinese case study, of an infant (55 days old) with coronavirus infection, presented with heart damage, pneumonia, and injury to the liver, which was confirmed via occasional arrhythmias as well as a myocardial zymogram. A small case series including a 13-month-old infant reported the development of heart failure along with multi-organ failure.<sup>38</sup>

A French case series reported acute myocarditis as well as systemic inflammation succeeding viral infection in 20 children who were critically ill. Significantly elevated levels of immunoglobulin (IgG and IgA) were observed, suggesting a postviral immunological reaction that causes myocardial damage. A notable decrease was observed in the levels of inflammatory biomarkers as well as an enhancement in the functioning of the cardiac system post-treatment with IVIG.<sup>39</sup>

### 2.3.1 | Acute heart failure

A few critical heart failure cases were reported linked to MIS-C. The cases had shown abdominal and GI as the presentations instead of chest pain. High fever with intense asthenia was observed in all children. When a larger population was considered, blood flow dynamics during admission to the ICU for paediatrics were low systemic blood pressure (BP) with shock and respiratory distress, causing immediate initiation on the ventilator.<sup>38</sup>

Pro-inflammatory and regulatory T cells, which induce a cytokine storm, have been suggested to generate myocardial and lung injury caused by COVID-19.<sup>40</sup>

In a retrospective study, only six children out of a total of 35 cried of chest discomfort in which the ECG conducted was not distinct, and only one patient had ST-segment elevation. The average lag amongst the initial clinical symptoms and heart failure symptoms was 6 days. Many patients were admitted immediately to the ICU; six patients, who were initially admitted to the general paediatric, had to be moved immediately after their condition worsened on the first day itself. On admittance to the ICU, two-thirds required invasive mechanical ventilation due to the development of respiratory distress, whereas 80% of them of patients required intravenous

inotropic drugs due to being in cardiogenic shock and mechanical circulatory assistance with oxygen through the veno-arterial extracorporeal membrane, which was favourably taken out in all.<sup>38</sup>

A single-centre retrospective study organised at the Birmingham Children's Hospital also reported the involvement of the cardiac system in COVID-19 infection.<sup>38</sup>

On echocardiogram, ECG abnormalities were found in nine patients (60%). Six of them had their ECGs normalised before discharge, which took an average of 5 days.<sup>40</sup>

### 2.3.2 | Coronary artery defects

Seven had prominent coronary arteries on echocardiography, but 14 patients had coronary artery defects on regular measurements, amongst which six patients had ectatic dilated coronaries. One patient had a moderate right coronary artery (RCA) fusiform aneurysm and a mild left anterior descending artery fusiform aneurysm (LAD).

### 2.3.3 | Atrioventricular valve regurgitation

Thirteen patients had atrioventricular valve regurgitation (AVVR) at the time of admission, with 10 of them having mitral regurgitation. Seven of the 10 patients showed improvement over time, with a median of 2 days. Nine patients had nonphysiological tricuspid regurgitation (mild-moderate), with five of them improving during the first day of care. Seven patients had nonphysiological AVVR at the time of discharge. Valve stenosis was not present in any of the patients.

The ejection fraction of the left ventricle was decreased (80%) in 12 patients, nine at the time of presentation and three after admission. The lowest LVEF was 44% for those with impaired function. On diagnosis, one patient had a serious disability (LVEF 28%), but he had improved to moderate impairment (LVEF 53%). Three of the patients had mild disabilities, which had all improved by the time they were discharged. The remaining eight patients had moderate disability, with seven of them having normalised LVEF at discharge and one having an EF of 50%. In these 10 patients, LVEF normalisation took an average of 4 days. Altered functioning of the left ventricle, involvement of the coronary artery and valve regurgitation indicate a considerably high probability of cardiac involvement than the French study.<sup>40</sup>

## 2.4 | Acute kidney injury

According to a hospital in the United Kingdom, including 52 paediatric patients, 46% of the patients had an increase in serum creatinine levels than the upper limit of reference interval (ULRI). At the same time, 29% of the patients met the specific requirement for BAPN criteria, used for diagnosis of acute kidney injury (AKI). The majority of these cases were observed in ICU patients and patients suffering from Paediatric Inflammatory Multisystem Syndrome (PIMS-TS),

which were 93% and 73%, respectively. Prerenal involvement was indicated as most of the patients presented with vomiting and diarrhoea. Additionally, 33% of the patients with AKI also had enlarged kidneys (>95% for age in bipolar length), observed using renal ultrasound.<sup>41</sup>

The proposed mechanism for AKI is through the binding of angiotensin-converting enzyme 2 (ACE2) with the spike (S) of viral protein, which causes activation of the angiotensin II. Priming and cleavage of the S protein take place by transmembrane protease serine 2 (TMPRSS2), which releases the viral fusion peptides and further facilitates fusion of the membrane. Simultaneous expression of TMPRSS2 and ACE2 in straight tubular cells and podocytes (observed using transcriptase analysis) is suspected of having a significant role in the entry of the virus into the cells of the host. Hence, a cytopathic action is exerted on the cells of the kidney due to the intrusion of the virus.<sup>42</sup>

Conclusively, most of kidney injury is believed to be caused due to a hyperinflammatory and hypovolemic shock. Improvement in kidney function was seen with the use of inotropic agents and fluid replacement.

The median level for serum creatinine dropped from 133  $\mu\text{mol/L}$  at presentation to approximately 63  $\mu\text{mol/L}$  after 4 days of being admitted to the hospital. Just four of the patients suffering from AKI had underlying complications, and none had received immunosuppressive agents.<sup>41</sup>

## 2.5 | Neurological manifestations

Four cases of children confirmed with coronavirus were observed with neurological symptoms, inclusive of muscle weakness, headaches, cerebellar signs, encephalopathy, reduced reflexes and brainstem.<sup>43</sup>

An important note in the group were the splenic lesions that were acute and observed on neuroimaging in all four patients. Moreover, as respiratory symptoms were less common in this group and, in case observed, were mild and quickly missed as records of children infected with coronavirus disease without symptoms are increasing; hence, coronavirus must also be acknowledged in paediatric cases showing neurologic symptoms without systemic engagement.

On the other hand, the neurological side effects might be important for the systemic autoinflammatory infection with regards to the raised systemic inflammatory markers.<sup>44</sup>

### 2.5.1 | Neuroimaging manifestations

One patient in Saudi Arabia, one patient in Peru, two patients in India, four patients in Argentina, four patients in Brazil, five patients in the United States and 13 patients in France all had neurological disorder linked to the COVID-19 infection. Neuroimaging anomalies ranging from moderate to severe were found to be recurrent patterns

of disease. Sixteen patients were seen with postinfectious immune-mediated acute disseminated encephalomyelitis-like changes in the brain neural enhancement, and eight patients were seen with myelitis, which were the most popular imaging trends. Even if there are no neurological signs, cranial nerve enhancement will occur. Children with MIS-C were prone to have myositis (four patients) and splenic lesions (seven patients). Cerebrovascular complications in children were less common than in adults. There were no significant pre-existing conditions, and the majority of the children had positive results. Moreover, in four of the previously healthy children, the emergence of fatal atypical CNS co-infections was observed.<sup>45</sup>

An analysis of the reports (recognised by the Columbia University Irving Medical Center Institutional Review Board) reveals that 43% of 82 children (aged 5 days to 18 year olds) were admitted with confirmed lab reports of coronavirus exhibited neurological symptoms. Headache (34%), fatigue or malaise (25%), altered mental state (23%), exhaustion (14%) and epilepsy (11%) were the most frequent signs. Three patients had cranial nerve VI palsies, which was noteworthy. Intracranial hypertension was also present in two of these patients. Although two patients had dysgeusia or ageusia, and only one of them had a stroke, the median patient age was 9 years, which may affect the kinds of signs experienced by these kids and what is explained by their parents. Twelve (34%) of patients with neurological signs had PCR evidence of active covid-19 infection, 19 (54%) had a positive antibody screen, and four (11%) were PCR- and antibody-positive at the same time.<sup>46</sup>

## 2.6 | Respiratory complications

A multicenter study organised in 11 paediatric hospitals in Italy and recruiting 168 patients reported the development of multiple complications in 33 patients, including interstitial pneumonia (26 patients), peripheral vasculitis (one patient) and severe acute respiratory illness (14 patients). Additionally, co-infection with a virus was reported in 10 of the patients; two patients had Epstein-Barr virus, one patient was seen with influenza A virus, three patients had rhinovirus, three patients were also observed with respiratory syncytial virus and non-SARS coronavirus infection. Co-infection with *Streptococcus pneumoniae* was also reported.

The most typical result amongst children who had blood tests was an elevation in CRP over 0.5 mg/dL (47/121), although other changes were seen in adults, such as neutropenia, leukopenia, lymphopenia, neutropenia and elevated LDH or CK values, were uncommon.<sup>47</sup>

## 2.7 | Septic shock

Evidence from a study conducted in Geneva, Switzerland, reported the characteristics of septic shock in three paediatric patients.

A 12-year-old Hispanic male suffering from asthma and obesity was the first patient. He had odynophagia, cough, fever, dyspnoea

and headache for 1 day. Inflammatory markers were not elevated in laboratory studies, but lymphocytopenia was discovered. When the patient was receiving treatment in the emergency room, an increase in tachycardia up to 170 beats per minute was seen, and he also presented with symptoms of compensated shock, including cold extremities, a 6-s capillary refill period and a 41 mmol/L lactate concentration.

A previously healthy 10-year-old with mixed race (white and Asian) suffering with obesity was the second patient. He had a fever of 40°C for 5 days and cough, vomiting, abdominal pain and odynophagia. Physical examination revealed a sick but not toxic patient who was conversant but slightly nervous, well-hydrated, tachycardic to 120 beats per minute, with low BP (85/50 mm Hg), tachypnea (respiratory rate 36 breaths per minute) and oxygen saturation of 89%-95% at normal room environment. COVID-19 hypotensive septic shock accompanied by multiorgan dysfunction syndrome (MODS) was the final diagnosis.

After 7 days of emesis, fever and extreme abdominal pain, the third patient, a previously stable 10-year-old Black male with obesity, emerged in hypotensive shock. He was found to be conscious and oriented with presence of tachypnea (respiratory rate was 39 breaths per minute) and tachycardia (117 breaths per minute). It was accompanied by systolic hypotension (85 mm Hg) even after administration of 20 mL/kg of crystalloid volume bolus prior to hospitalisation. An oxygen saturation of 98% was being maintained at normal room environment. Also, elevation in inflammatory parameters and lactate concentrations (40 mmol/L) was observed accompanied by the presence of lymphocytopenia.<sup>48</sup>

## 2.8 | Ophthalmic manifestations

A case report from China reported the development of dermatitis on eyelids and conjunctivitis in a 2-year-old patient. The manifestations affecting the eye got resolved within 5 days of receiving treatment. Due to the lack of evidence, it was suspected to be caused due to low body resistance because of the systemic COVID-19 infection leading to secondary bacterial infection.<sup>49</sup>

### 2.8.1 | Optic neuritis

A previously healthy 10-year-old girl with a positive COVID-19 PCR test result was admitted to the hospital with 2 days of lack of vision in her left eye. She has no prior history of fever, eye pain, vomiting, headache, epilepsy or injuries. Her medical assessment findings and her inflammatory markers, including CRP, procalcitonin, D-dimer, ferritin and lactate dehydrogenase levels, were all within normal ranges. Her visual acuity in her left eye was slightly compromised and regular in her right eye. She did not have any specific neurological disorders, and her systemic test results were unexceptional. A paediatric ophthalmologist examined her and determined she had optic neuritis of the left eye. A paediatric neurologist advised her to get an MRI scan of her head, spine and orbit. The diagnosis of left optic neuritis was then confirmed by the orbit's MRI, which showed

moderate enlargement and minor T2 hyperintensity of the left optic nerve's intracanalicular and intraorbital segments.<sup>50</sup>

## 2.9 | Dermatological manifestations

### 2.9.1 | Chilblains

Acute chilblains have been reported as a complication of coronavirus in paediatrics and teenagers.<sup>51</sup> It is understood that it is a localised inflammatory condition due to a maladaptive vascular response to nonfreezing low temperature.<sup>52</sup> It is most common in women and middle-aged adults and seems to be uncommon in children.<sup>52-55</sup>

In a retrospective study involving 22 children and teenagers, lesions were noted that were clinically like chilblains. These patients, who had no predisposing factors or previous history of chilblains, presented the symptoms in a short duration of time during the warm weather. Cases were reported during the peak of the coronavirus in places such as Madrid and other profoundly affected places. In 59% of the reports, being in close contact with an asymptotically affected adult was seen and the cases having mild or moderate disease. In 55% of the reports, chilblains were the only symptoms seen, and 45% had mild presentations that may be due to coronavirus.<sup>51</sup>

In such cases, chilblains were detected after an average of 16 days from the initial symptoms. Only one patient out of the 19 tested patients was PCR positive for the coronavirus disease. However, the sensitivity of the test may be low in mild cases and paediatrics, which could be due to a lesser viral load—considering that the positivity of the PCR is about 11.2% in paediatrics requiring to be admitted into the hospital for coronavirus.<sup>56</sup>

On the other hand, chilblains could have been detected much later in the disease duration, and thus, the PCR test may have turned negative when conducted.<sup>51</sup>

### 2.9.2 | Chilblain-like lesions

In one Italian study, video capillaroscopy was used to examine 19 teenagers.<sup>57</sup> Even though the skin lesions were confined to the feet, capillary abnormalities of the fingers and toes were defined. Microhemorrhages accompanied by peripheral edema were the most common presentation, whereas dilation of capillaries was seen in both the toes and fingers. COVID 19 chilblains may be a result of systemic interference rather than being caused because of local causes. Furthermore, these characteristics tend to be more extreme than those seen in idiopathic chilblains, with absence of microhemorrhages.<sup>58</sup>

### 2.9.3 | Erythema multiforme

In a case report, a 17-year-old patient presented with isolated acral papules and targetoid lesions.<sup>59</sup> In another study, four patients with chilblain-like lesions also had associated EM, with both true target

and targetoid lesions; one of the children tested positive for the COVID-19 infection through results of PCR, and skin biopsies taken in two of the cases revealed endothelial positive immunohistochemistry stain to SARS-CoV-2 spike protein.<sup>60</sup> A positive COVID-19 PCR result was found in a 6-year-old boy with acral target lesions of erythema multiforme (EM), conjunctivitis and serious, painful cheilitis.<sup>61</sup>

Full clinical analysis showed skin lesions associated with EM affecting the palms, feet, forearms, elbows, arms, calves, thighs, hips and ears in four Spanish children with chilblains on the feet, two of whom also had involvement of the hands.<sup>62</sup> An Italian patient also developed skin target lesions of EM after chilblains.<sup>63</sup>

### 2.9.4 | Varicella-like exanthem

A case series conducted in Italy provided information about an 8-year-old patient that presented with varicella-like exanthem as a COVID-19 specific skin manifestation.<sup>64</sup>

### 2.9.5 | Peripheral vasculitis

Several reports have shown rounded, well-circumscribed erythematous or violaceous plaques or nodules, chilblain-like lesions and diffuse digital erythema on the dorsal surfaces of the toes in patients with COVID-19,<sup>65,66</sup> ranging from asymptomatic or mild to rapidly progressing disease.<sup>67</sup> In the absence of COVID-19 pneumonia, however, skin lesions are a common finding in children and younger adults. These patients' COVID-19 skin lesions display vasculitic changes, such as perivascular cuffing and inflammatory lymphocytic infiltration, which could lead to luminal thrombosis.<sup>68,69</sup> In one study, a child with chilblains showed asymptomatic fundoscopic changes typical of retinal vasculitis, which is synonymous with a predominant vasculitic condition.<sup>70</sup>

In addition, a sole case of peripheral vasculitis was reported in a case study conducted in Italy.<sup>47</sup>

## 2.10 | Thrombotic microangiopathy

We suspected that complement activation is a significant factor in COVID-19 in the paediatric population and wanted to know whether these patients had thrombotic microangiopathy (TMA). We admitted 50 hospitalised paediatric patients with acute COVID-19 infection ( $n = 21$ , moderate COVID-19;  $n = 11$ , serious COVID-19) or MIS-C ( $n = 18$ ). Soluble C5b9, also known as the soluble membrane attack complex (sMAC), was tested in plasma as a biomarker of complement activation and TMA, and the increase was observed in patients with minimal disease, serious disease and MIS-C relative to 26 stable control subjects. Increased sC5b9 levels were linked to higher serum creatinine levels but not to age. Of the 19 patients for whom full clinical requirements were available, 17 patients met TMA criteria. A high% of children with SARS-CoV-2 infection tested positive for complement activation and followed clinical and diagnostic requirements for TMA.<sup>71</sup>

TABLE 1 The table contains a summary of the studies that were included in this paper

Author name	Study population	Cases reported	Study design	Complication	Age group (years)	Country	Month and year published
1. Buonsenso et al <sup>33</sup>	129	68	Cross-sectional	Long COVID	<18 years	Italy	April 2021
2. MIS-C							
Webmd (Accessed 26 Dec 2020) <sup>73</sup>	102	50	Case reports	PIMS MIS-C	<18 years	US and European countries	May 2020
Mamishi et al <sup>37</sup>	45	45	Retrospective	MIS-C	<21 years	Iran	Aug 2020
Feldstein et al <sup>29</sup>	186	186	Retrospective study	MIS-C	<21 years	USA	July 2020
Belhadjer et al <sup>38</sup>	35	6	Retrospective study	AHF	2-16 years	France, Switzerland	May 2020
Ramcharan et al <sup>40</sup>	15	14 & 13	Retrospective study	Coronary artery defect & Atrioventricular valve regurgitation	6-11 years	England	June 2020
3. Stewart et al <sup>39</sup>	52	15	Retrospective study	Renal dysfunction (AKI)	0-16 years	London, UK	June 2020
4. Cardiovascular complications							
Cui et al <sup>41</sup>	1	1	Case report	Arrhythmia	55 days old	China	March 2020
Grimaud et al <sup>42</sup>	20	20	Case series	Acute myocarditis	<18 years	France	June 2020
5. Neurological manifestations							
Lindan et al <sup>45</sup>	38	38	Survey	Neuroimaging manifestations	0-18 years	China	March 2021
Lin et al <sup>46</sup>	82	35	Retrospective	Neurological symptoms	<18 years	USA	Jan 2021
Abdel-Mannan et al <sup>43</sup>	27	4	Case series	Neurological symptoms	<18 years	London, UK	July 2020
6. Garazzino et al <sup>47</sup>	168	40	Cross-sectional	Respiratory complications	0-17 years	Italy	May 2020
7. Dalian et al <sup>48</sup>	57	3	Retrospective study	Septic shock	10-12 years	Switzerland	May 2020
8. Ophthalmic manifestations							
Wu et al <sup>49</sup>	1	1	Case report	Ophthalmic	2 years 10 month	China	April 2020
Parvez et al <sup>50</sup>	1	1	Case report	Optic neuritis	10 year	UAE	March 2021
9. Dermatological manifestations							
Andina et al <sup>51</sup>	22	22	Case series	Chilblains	<18 years	Spain	May 2020
El Hachem et al <sup>57</sup>	21	19	Prospective study	Chill blain like lesions	11-17 years	Italy	May 2020
Janah et al <sup>59</sup>	1	1	Case report	Erythema multiforme	17 years	Morocco	May 2020
Labé et al <sup>61</sup>	1	1	Case report	Erythema multiforme	6 years	France	May 2020
Torrel et al <sup>60</sup>	4	4	Case reports	Erythema multiforme	11-17 years	Spain	May 2020
Mazzotta et al <sup>63</sup>	1	1	Case report	Erythema multiforme	9 years	Italy	June 2020
Valerio et al <sup>64</sup>	22	1	Case series	Varicella-like exanthem	-	Italy	April 2020
Garazzino et al <sup>47</sup>	1	1	Case report	Periphereal vasculitis	0-17 years	Italy	April 2020
Quintana-Castanedo et al <sup>70</sup>	1	1	Case report	Periphereal vasculitis	11 years	Spain	Dec 2020
10. Diorio et al <sup>71</sup>	50	17	Prospective	Thrombotic microangiopathy (TMA)	<18 years	USA	Dec 2020
11. Vania et al <sup>72</sup>	127	4	Retrospective study	Gastrointestinal symptoms	<18 years	Italy	Oct 2020
12. DKA							
Han et al <sup>73</sup>	7	7	Retrospective study	Diabetic ketoacidosis (DKA)	<18 years	Korea	Feb 2021
Jafarpoor et al <sup>74</sup>	1	1	Case report	Diabetic ketoacidosis (DKA)	9 years old	Iran	Aug 2020

## 2.11 | GI symptoms

At least one comorbidity was present in 20 of the 127 patients, amongst which five had a chronic heart illness, four had a GI disorder, three were obese, and two each had chronic kidney disease, chronic neurologic disorder and immunologic syndrome. Only one medically complicated patient was included (defined as children who needed long-term life support). The distribution of comorbidities did not vary by severity class. Furthermore, the prevalence of ICU admission was equivalent in patients with and without comorbidities. Fever, cough and rhinorrhea were the most frequent symptoms recorded on admission. Seventy-seven of the 127 patients had respiratory problems (cough, rhinorrhea, wheezing and dyspnea). Thirty-six people out of 127 had GI signs (vomit, diarrhoea and stomach pain), with 28 having diarrhoea, 12 vomiting and eight having abdominal pain.<sup>72</sup>

## 2.12 | Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) in paediatric patients without direct infection has been linked to the COVID-19 pandemic. DKA cases were seen to be recorded during the COVID-19 outbreak, as was the incidence of polydipsia, which was considerably higher. Polydipsia and polyuria were present in all seven patients admitted during the COVID-19 pandemic (100%), and they were newly diagnosed with diabetes mellitus (DM). Most of the patients had three main diabetes symptoms including polydipsia, polyuria and weight loss, with 100%, 100% and 85.7% of the patients, respectively, displaying polydipsia, polyuria and weight loss. Polyuria was significantly more common during the COVID-19 century. Four patients in the overall cohort had previously been diagnosed. Four patients in the overall cohort had already been diagnosed with diabetes, whereas 15 were newly diagnosed. All seven DKA patients admitted to the ER had recently been diagnosed with DM.<sup>73</sup>

A 9-year-old boy was admitted for appendectomy and diagnosed with stomach pain, nausea, vomiting, restlessness, lethargy and cough, according to a case study. After lab tests revealed that BS had risen (after 8 hours), and the patient had symptoms of restlessness, fatigue, lethargy and cough, the patient was diagnosed with DKA. A nasal swab RT-PCR test for COVID-19 was performed, and a positive diagnosis was obtained. A chest CT scan revealed multifocal bilateral patchy consolidation, confirming the diagnosis.<sup>74</sup>

## 3 | CONCLUSION

The recent outbreak of COVID-19 has had a major impact on both the adult and paediatric population. However, the paediatric population, as seen above, has affected children in many ways. Paediatricians all over the world are concerned that this may have longer-lasting effects on the paediatric population, especially in the coming days due to the unpredictable mutations of the virus. A compilation of

our results (Table 1) indicated MIS-C to be the most prevalent of the complications and the root cause of many other complications, as it affects multiple organs due to the aggravated inflammatory response of the body. The least prevalent were found to be septic shock and ophthalmic complications. Childhood is a fragile and crucial time in one's life when behavioural, social and educational development takes place. The evidence that COVID-19 may have a long-term effect on children, particularly those with asymptomatic COVID-19, emphasises the importance of paediatricians, mental health specialists and authorities responsible for policymaking to enforce measures to minimise the pandemic's impact on the health of children.

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## DISCLOSURE

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in PubMed at <https://doi.org/10.25504/FAIRsharing.a5sv8>.

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